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Design and Synthesis of Potent and Selective BACE-1 Inhibitors†

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Highly potent BACE-1 protease inhibitors have been developed from an inhibitors containing a hydroxyethylene (HE) core displaying aryloxymethyl or benzyloxymethyl P1 side chain and a methoxy P1′ side chain. The target molecules were synthesized in good overall yields from chiral carbohydrate starting materials. The inhibitors show high BACE-1 potency and good selectivity against cathepsin D, where the most potent inhibitor furnishes BACE-1 $K_i \ll 1$ nM and displays > 1000-fold selectivity over cathepsin D.

1. Introduction

Alzheimer's disease (AD[a]) is a disabling, progressive, and ultimately fatal form of dementia afflicting approximately 40% of the population over 80 years, with over 30 million people suffering from AD worldwide.[1,2] The neuropathological features of AD are complex, but one of the major factors associated with AD is the buildup of amyloid plaques and neurofibrillary tangels in the brain tissue.[3] The primary component of the amyloid plaques is aggregated amyloid-β (Aβ) which is the cleavage product of amyloid precursor protein (APP), a transmembrane protein,[3] by the action of β- and γ-secretase. In vitro, the aggregation state of Aβ has been shown to influence neurotoxicity,[4,5] and in neuritic plaque found in the brain of AD patients, amyloid-β42 (Aβ1-42) dominates.[6]

BACE-1 knockout mice, transgenic for human APP, do not show any apparent adverse phenotype or any Aβ buildup in the brain.[7−9] These data have helped to validate BACE-1 as a suitable drug target for Alzheimer's disease and have led to an intense search to identify safe and efficacious drugs based on selective BACE-1 inhibition.[10−15]

Several groups have reported on BACE-1 inhibitors containing substituted isophthalamides as highly promising P2-P3 groups.[10] Recently Stachel et al. reported that 5-substituted isophthalamides coupled to HEA cores furnish potent and selective BACE-1 inhibitors.[16] One of these inhibitors, **2** (Figure 1), displayed an IC_{50} of 11 nM.

Here, we describe a novel hydroxethylene (HE) motif, readily available from chiral carbohydrate precursors and displaying aryloxymethyl or benzyloxymethyl P1 side chain and a methoxy group as the P1′ side chain, that furnishes highly potent BACE-1 inhibitors and inhibitors displaying good to excellent selectivity over the antitarget cathepsin D.[17] These new HE scaffolds have been investigated using the 5-substituted isophthalamide moiety of inhibitor **2** or using a di-*N*-propylisophthalamide in the P2-P3 position.[16,18] The most potent inhibitor discovered in this series, **1d** (Figure 1), exhibits an impressive BACE-1 IC_{50} of 0.3 nM and $K_i \ll 1$ nM, hence, > 1000-fold selectivity over cathepsin D. Insertion of an oxygen atom at P1′ improved activity versus BACE-1 and selectivity versus cathepsin D, compared with inhibitor **3** previously synthesized in our laboratory having a P1′ methyl group.

2. Result and Discussion

2.1. Chemistry. The target compounds **1a**−**l** were prepared as outlined in Schemes 1 and 2. The diol **4**[19−21] was reacted with dibutyltin oxide in refluxing toluene, furnishing the tin acetal which was subsequently reacted with either 4-bromobenzyl bromide or 3,5-difluorobenzyl bromide in the presence of tetrabutylammonium bromide, yielding the two corresponding benzylated products **5a** and **5b** in 87% and 78% yields, respectively (Scheme 1).[22] For the synthesis of **5c**−**e**, the diol **4** was treated with triphenylphosphine (Ph_3P) and diisopropyl azodicarboxylate (DIAD) in dichloroethane (DCE), furnishing epoxide **6** in 49% yield.[22] Epoxide **6** was then reacted with 4-bromophenol, 3,5-difluorophenol, or phenol in *N*,*N*′-dimethylformamide (DMF) in the presence of K_2CO_3, giving **5c**−**e** in 81%, 71%, and 75% yields, respectively.[23] In all the following reaction steps the same synthetic procedures were employed irrespective of 6-O-substituents. Compounds **5a**−**e** were thus converted to the corresponding 5-azides **7a**−**e** with inversion of configuration using Ph_3P, DIAD, and diphenylphosphoryl azide (DPPA) in tetrahydrofuran (THF) in 68%, 88%, 90%, 58%, and 68% yields, respectively.[22] Hydrolysis of the 1,2-*O*-isopropylidene acetal in **7a**−**e** followed by glycosylation was performed using HCl in methanol (1 M), formed by in situ

†The PDB deposition codes for the BACE-1 complex crystal structures with inhibitor **1d** is 3IXJ.

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[a]Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; APP, amyloid precursor protein; BACE-1, β-site amyloid precursor protein cleaving enzyme; Cath D, cathepsin D; HE, hydroxyethylene.

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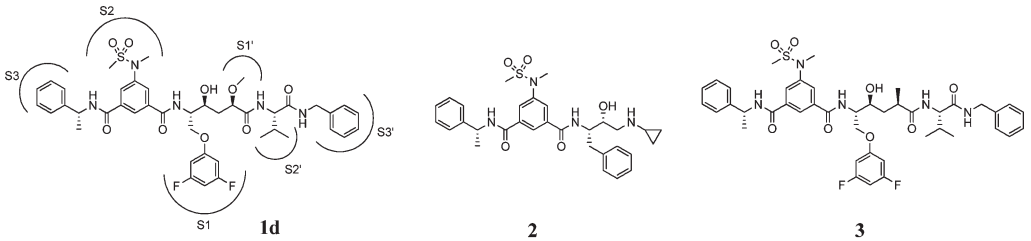
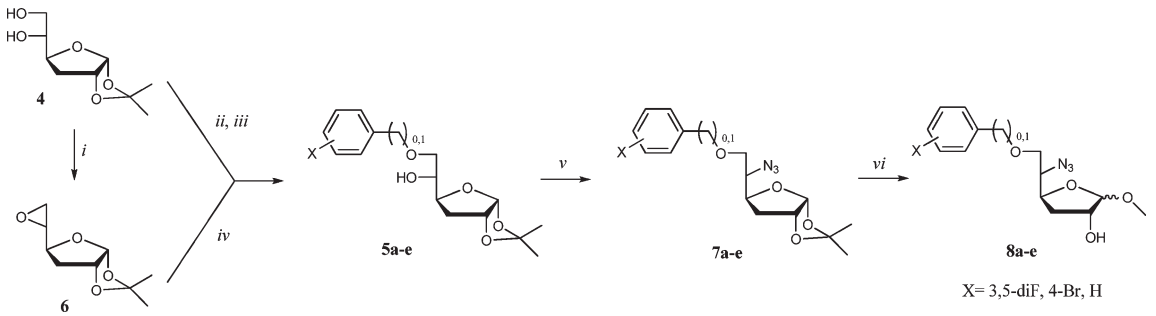


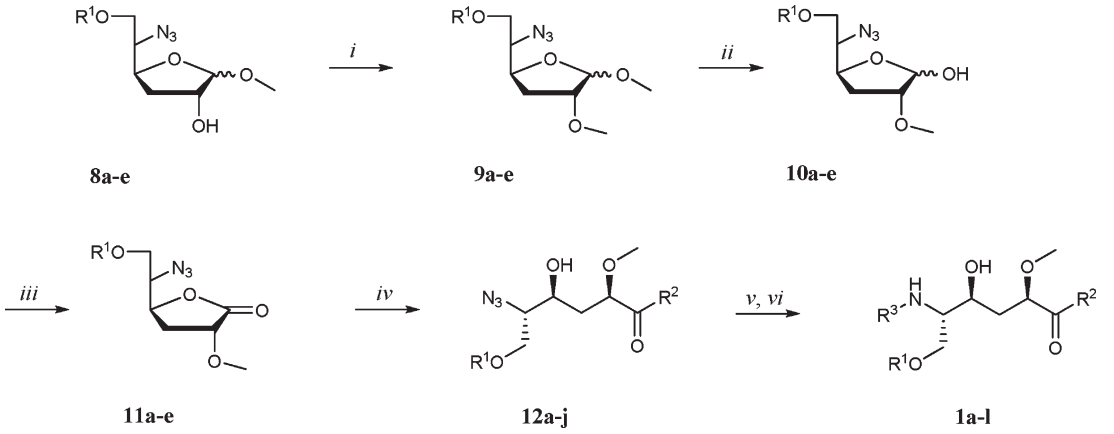
Figure 1. HEA (**2**) and HE (**1d**, **3**) BACE-1 inhibitor K_i or IC_{50} and their cathepsin D selectivities.

Scheme 1[a]



[a] Reagents and conditions: (i) Ph_3P, DIAD, DCE, reflux; (ii) Bu_2SnO, toluene, reflux; (iii) tetrabutylammonium bromide, 4-bromobenzyl bromide, or 3,5-difluorobenzyl bromide, toluene, 90 °C; (iv) 4-bromophenol or 3,5-difluorophenol or phenol, K_2CO_3, DMF, 120 °C; (v) Ph_3P, DIAD, DPPA, THF, room temp; (vi) HCl, MeOH, room temp.

Scheme 2[a]



[a] Reagent and conditions: (i) MeI, Ag_2O, DMF, room temp; (ii) H_2SO_4, 1,4-dioxane, reflux; (iii) PDC, DCM, room temp; (iv) R_3NH_2 (**I**, **II**, **III**, **IV**, **V**, or **VI**), 2-hydroxypyridine, DIPEA, 70 °C; (v) Ph_3P, H_2O, MeOH; (vi) R_4COOH (**A** or **B**), Py-BOP, DIPEA, DCM, room temp.

addition of acetyl chloride to methanol at 0 °C,[19] delivering the methyl glycosides **8a**−**e** as anomeric α/β mixtures in 87%, 76%, 95%, 85%, and 98% yields, respectively.

The conversion of the methyl glycosides **8a**−**e** into the target compounds **1a**−**l** was achieved over several steps as shown in Scheme 2. Methylation at the 2-O-position in **8a**−**e**, using methyl iodide in the presence of Ag_2O in DMF, furnished the methyl glycosides **9a**−**e** in 96%, 77%, 90%, 64%, and 90% yields, respectively.[24] Hydrolysis of the methylglycosides in refluxing 1,4-dioxane in the presence of sulphuric acid for ∼1 h followed by quenching with aqueous sodium carbonate afforded the desired products **10a**−**e** in 69%, 63%, 81%, 97%, and 59% yields, respectively.[25] Subsequent oxidation at the anomeric position using pyridinium dichromate in dichloromethane (DCM) gave the corresponding lactones **11a**−**e** in 66%, 68%, 59%, 63%, and 72% yields, respectively.[26] The lactones **11a**−**e** were ring-opened with (*S*)-2-amino-*N*-benzyl-3-methylbutyramide (**I**) (see Figure 2) upon heating in diisopropylethylamine (DIPEA) using 2-hydroxypyridine as an activator of the lactone to give the ring-opened amides **12a**−**e** in 85%, 82%, 96%, 97%, and 30% yields, respectively.[27] The lactone **11d** was also ring opened using amines **II**, **III**, **IV**, V, and **VI**, employing the same protocol (vide supra) to give product **12f**−**j** in 82%, 80%, 79%, 39%, and 43% yields, respectively. The amine **I** was synthesized from

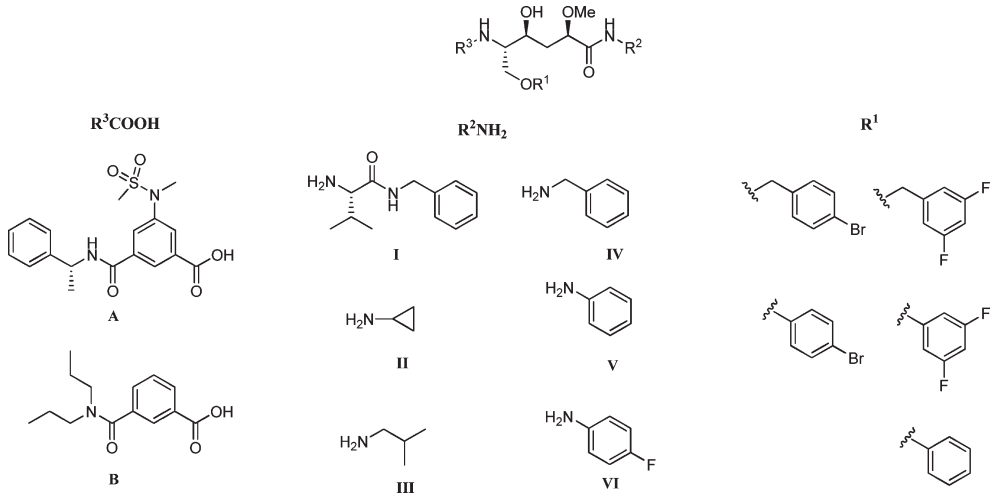
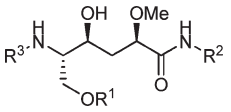
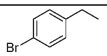


Figure 2. R^3 carboxylic acids, R^2 amine, and R^1 ether library.

Table 1. Target Compounds and Inhibition Data



Compd	R^1	R^2	R^3	K_i (nM) BACE	K_i (nM) Cath D
1a		**I**	**A**	60	ND[a]
1b		**I**	**A**	80	ND
1c		**I**	**A**	75	840
1d		**I**	**A**	<<1	1100
1e		**I**	**A**	9	460
1f		**II**	**A**	1800	>5000
1g		**III**	**A**	400	>5000
1h		**IV**	**A**	1400	>5000
1i		**V**	**A**	200	>5000
1j		**VI**	**A**	100	>5000
1k		**I**	**B**	>10000	34% (79%)[b]
1l		**I**	**B**	220	52% (85%)[b]

[a] ND = not determined. [b] Inhibition at an inhibitor concentration of 0.5 μM (5 μM). K_i values are the mean from two different experiments.

Boc-Val-OH and benzylamine (see Supporting Information), and the amines **II**−**VI** were commercially available. Reduction of the azide group in **12a**−**j** was achieved using Ph_3P in methanol containing a few drops of water, providing the corresponding amines which were coupled without prior purification with carboxylic acids **A** and **B**[16,18,28] using benzotriazole-1-yloxytris-(pyrrolidino)phosphonium hexafluorphosphate (Py-BOP) and DIPEA in DCM,[22,29] furnishing the 12 target compounds **1a**−**l** in yields of 30−81%.

2.2. Structure−Activity Relationships. We have previously disclosed that a novel HE motif incorporating a methylaryloxy or methylbenzyloxy P1 substituent that coupled to the previously reported 5-substituted isophthalamide (**A**)[16] in the P2-P3 position furnishes highly potent BACE-1 inhibitors, e.g., inhibitor **3** with a K_i of 1 nM.[30] A potential drawback with this inhibitor series is the apparent low selectivity toward cathepsin D, for which **3** displays a K_i of 59 nM, furnishing a modest 60-fold shift in K_i over cathepsin D. To optimize potency and cathepsin D selectivity for this inhibitor series, we have examined the S1′ pockets of BACE-1 and cathepsin D probing for potential discriminating molecular features. The comparisons were made using the 1LYB[31] 3D structure of cathepsin D and the 3DM6[32] 3D structure for BACE-1. While the methyl group has frequently been used as a P1′ residue in HE template, the S1′ pocket of BACE-1 can accommodate larger groups. Moreover, the S1′ pocket of BACE-1 can also accommodate polar interactions from the side chains of Thr72 and Asp228, in contrast to the S1′ pocket in cathepsin D which comprises only hydrophobic residues.

On the basis of this observation, we introduced a methoxy P1′ side chain, which is still a small group but more polar than the P1′ methyl side chain (inhibitor **3**). We noted that not only was the potency enhanced, delivering a BACE-1 inhibitor with $K_i \ll 1$ nM, but also that the selectivity against cathepsin D was dramatically improved (K_i of 1100 nM for cathepsin D). The natural substrate, APP, of BACE-1 has a polar Asp in the P1′ position,[33] and while it has previously been reported[34] that selectivity over cathepsin D can be enhanced by increasing the polarity of the P1′ side chain, the BACE-1 inhibitors reported on displayed only weak inhibitory activities with K_i in the low micromolar range. Following this result a broader SAR study of this HE scaffold with a P1′ methoxy side chain was undertaken. With the Val-benzylamide P2′ group (**I**) reported by Ghosh et al.,[35] various P1 side chains were introduced into the HE scaffold (Table 1). It was soon apparent that with increased size of the P1 group from that of inhibitor **1d** a substantial loss in potency could be observed, i.e., inhibitors **1a**−**c** furnishing K_i of 60, 80, and 75 nM, respectively. Interestingly, when the 3,5-difluorophenoxymethyl P1 side chain of **1d** was replaced with the corresponding nonfluorinated and smaller P1 group, **1e**, a more than 10-fold loss in activity was observed (Table 1). Possibly the activity of the 3,5-difluorophenoxymethyl P1 side chain can be attributed to advantageous lipophilic interactions of the fluorine group with the overlapping S1−S3 pockets of BACE-1.

Having identified a highly potent P1 group, we also examined the P2-P3 group **B**[18] (Table 1), which previously has demonstrated modest nanomolar potency toward BACE-1 enzyme when coupled to a HE scaffold. Not surprisingly this P2-P3 group, lacking interactions with the S2 pocket, furnished substantially less potent inhibitors also with the present HE isostere, with inhibitors **1k** and **1l** displaying K_i of >10 and 0.22 μM, respectively. It has been reported that each oxygen of the sulfonamide of the P2-P3 group **A** contributes with hydrogen bonds to amino acids of the S2 pocket[36] which in part could account for the loss in potency observed for inhibitors **1k** and **1l**.

To reduce molecular weight and the number of amide bonds, we then examined the influence of replacing the P2′ Val-benzylamide group (**I**) with smaller substituents (Table 1). Of the selected lipophilic substituents in inhibitors **1f**−**j**, all were substantially less potent than lead inhibitor **1d**. The BACE-1 K_i for inhibitor **1j** (100 nM) and the slightly less active **1i** (600 nM) are, however, surprisingly good. The P2′ phenyl groups of **1i** and **1j** are based on modeling in a coplanar arrangement with the P1′-P2′ amide, and while occupying the S2′-pocket more efficiently with close contact interactions compared to the valine of **1d**, they also retain the important backbone hydrogen bonds to the carbonyl of Gly34 and the amide of Thr72. In contrast, the benzyl moiety of **1h** may disrupt these backbone hydrogen bonds while adjusting the conformation to fit in the S2′ pocket.

2.3. X-ray Crystallography Analysis. The high potency of this series, exemplified by the 3D crystal structure of inhibitor **1d**, is to a large extent due to the numerous hydrogen bonds formed between the inhibitor and the enzyme.

The 8 times improved potency of **1d** over **3** is likely due to improved interactions in the S1′ pocket where the P1′ methyl group of **3** does not have any close interactions with any of the S1′ residues. The closest residues are the polar side chains of Thr72 and Asp228. Introduction of a methoxy group in the P1′ position thus introduces close contact interactions with Tyr198 and Ile226 and makes it more suitable for the polar environment in the S1′ pocket of BACE-1. There are no direct hydrogen bonds; however, the ether oxygen is involved in an extensive hydrogen bond network, including water and the side chains of Thr72, Thr231, Arg235, and Thr329 (Figures 3 and 4).

3. Conclusions

In summary, we have developed a novel HE central core, incorporating a methoxy P1′ substituent and aryloxymethyl or benzyloxymethyl P1 substituents and delivering potent and cathepsin D selective BACE-1 inhibitors. The excellent potencies, together with the observations that inhibitors from this class can display high BACE-1 selectivity over cathepsin D, make further investigations highly warranted.

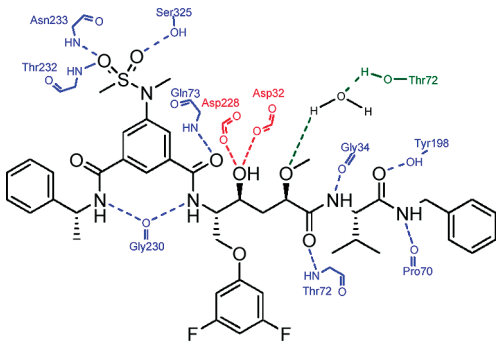


Figure 3. Overview of the hydrogen bonding network of inhibitor **1d**.

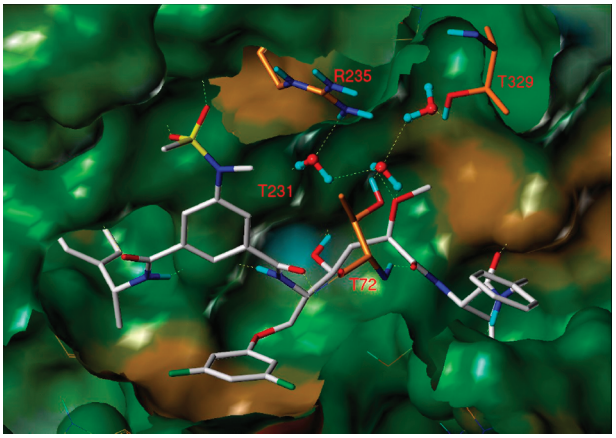


Figure 4. X-ray crystal structure of inhibitor **1d** in the active site of BACE-1 and its interactions with BACE-1 are depicted.

4. Experimental Section

4.1. Protease Enzyme Assays. The BACE-1 and cathepsin D assays were performed as previously described.[32]

4.2. Crystallography. The details of the crystallization and structure determination procedures have been published elsewhere.[32] Briefly, the complex of BACE-1 and **1d** was crystallized in the monoclinic space group *P*21 with cell dimensions (in Å) of $a = 81.9$, $b = 102.7$, $c = 100.4$ and $\beta = 103.4°$. The strucuture was determined to 2.2 Å resolution with an R of 0.21 ($R_{free} = 0.24$) and deposited in RCSB PDB (3IXJ).

4.3. General Methods. All glassware was dried over an open flame before use in connection with an inert atmosphere. Concentrations were performed under reduced pressure at < 40 °C (bath temperature). Thin layer chromatography was performed using Merck silica gel 60 F-254 plates with detection by UV, charring with 8% sulfuric acid or ammonium molybdate (100 g), Ce(IV) sulfate (2 g), sulfuric acid (10%, 2 L). Column chromatography was performed on silica (0.035−0.070 mm). NMR spectra were recorded at 25 °C on a Varian (300 or 400 MHz) or a Bruker (400 or 500 MHz) instrument using the solvent residual peak ($CDCl_3$ ^{1}H δ 7.26 and ^{13}C δ 77.17 or CD_3OD-d_4 ^{1}H δ 3.31 and ^{13}C 49.0) as standard. Unless stated otherwise, all materials were obtained from commercial suppliers and used without further purification. DCM was refluxed over CaH_2 and distilled and stored over 4 Å molecular sieves before use. Compounds **1a**−**l** were further purified before biological testings using preparative RP-HPLC, consisting of Waters 2767 autoinjector and fraction collector, Waters 996 photodiode array detector, and Micromass ZQ2000 mass detector (operated in +ESI). The preparative reversed phase column was an ACE C_8, 21 mm × 100 mm, 5 μm, 100A from ACE (U.K.), and the mobile phases were based on water/acetonitrile containing 0.1%TFA. The purity of final compounds was assessed by two different analytical LC−MS methods and found to be ≥95% in all cases. The LC−MS analyses were perfomed using a Waters LC−MS instrument equipped with a UV/vis detector, Waters 996 and a MS detector, Waters ZQ, using one of the following two methods. (1) Method A: column, ACE C_8, 50 mm × 3 mm, 3 μm particles; pump, Waters Alliance 2695; mobil phase A, 10 mM NH_4OAc in water; mobil phase B, 10 mM NH_4OAc in 90% acetonitrile; gradient, 20−100% B in 5 min followed by 2 min at 100% B. (2) Method B: as chromatography system A except for the following: mobil phase A, 0.2% HCOOH in water; mobil phase B, 0.18% HCOOH in 90% acetonitrile. Optical rotations were measured at room temperature on a Perkin-Elmer 341 polarimeter using a 10 cm, 1 mL cell.

4.4. Synthetic Procedures. 4.4.1. Synthesis of 5a,b. General Benzylation Procedure. The diol **4** (1 equiv) and dibutyltin oxide (1.32 equiv) were dissolved in toluene. The mixture was refluxed for 5 h with a Dean−Stark trap. The temperature was then lowered to 90 °C, and tetrabutylammonium bromide (1.32 equiv) and the appropriate benzyl bromide (1.27 equiv) were added. The mixture was stirred at 90 °C overnight. Then the solvent was removed under vacuum, and the residue was purified by column chromatography (toluene/ethyl acetate 10:1). **5a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, $J_{HH} = 8.3$ Hz, 2H), 7.20 (d, $J_{HH} = 8.3$ Hz, 2H), 5.79 (d, $J_{HH} = 3.7$ Hz, 1H), 4.73 (t, $J_{HH} = 4.2$ Hz, 1H), 4.55−4.45 (m, 2H), 4.24−4.18 (m, 1H), 4.01−3.95 (m, 1H), 3.60−3.55 (m, 1H), 3.49−3.44 (m, 1H), 2.09−2.03 (m, 1H), 1.88−1.79 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H); MS (ESI) m/z 395.1 ([M + Na]$^+$ calcd for $C_{16}H_{21}BrNaO_5^+$ 395.0).

4.4.2. Synthesis of 5c−e. General Epoxide Nucleophilic Opening Procedure. The epoxide **6** (1 equiv) and the appropriate phenol (2 equiv) were dissolved in DMF. K_2CO_3 (0.25 equiv) was added, and the mixture was heated to 110 °C and stirred at that temperature overnight. The solvent was removed by coevaporation with toluene. The residue was purified by column chromatography (toluene/ethyl acetate 20:1). **5c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $J_{HH} = 9.1$ Hz, 2H), 6.79 (d, $J_{HH} = 9.1$ Hz, 2H), 5.82 (d, $J_{HH} = 3.6$ Hz, 1H), 4.77 (t, $J_{HH} = 4.2$ Hz, 1H), 4.34−4.27 (m, 1H), 4.16−4.11 (m, 1H), 4.07−4.02 (m, 1H), 3.96−3.91 (m, 1H), 2.50 (bs, 1H), 2.18−2.13 (m, 1H), 1.94−1.85 (m, 1H), 1.51 (s, 3H), 1.32 (s, 3H); MS (ESI) m/z 381.0 ([M + Na]$^+$ calcd for $C_{15}H_{19}BrNaO_5^+$ 381.0).

4.4.3. Synthesis of 7a−e. General Azide Substitution Procedure. Compounds **5a**−**e** (1 equiv) and triphenylphosphine (1.3 equiv) were dissolved in THF. The mixture was cooled to −15 °C (ice/acetone). Diisopropyl azodicarboxylate (2.1 equiv) was added dropwise to the solution. The temperature was then increased to 0 °C, and diphenylphosphoryl azide (1.4 equiv) was added. The temperature was kept at 0 °C for an additional 30 min and then at room temperature overnight. The mixture was concentrated, and the residue was purified by column chromatography (toluene/ethyl acetate 30:1). **7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, $J_{HH} = 8.3$ Hz, 2H), 7.22 (d, $J_{HH} = 8.3$ Hz, 2H), 5.81 (d, $J_{HH} = 3.6$ Hz, 1H), 4.73 (t, $J_{HH} = 4.2$ Hz, 1H), 4.52 (s, 2H), 4.33−4.26 (m, 1H), 3.74−3.69 (m, 2H), 3.54−3.50 (m, 1H), 2.07−2.01 (m, 1H), 1.92−1.84 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H); MS (ESI) m/z 420.1 ([M + Na]$^+$ calcd for $C_{16}H_{20}BrN_3NaO_4^+$ 420.1).

4.4.4. Synthesis of 8a−e. General Hydrolysis and Glycolsylation Procedure. Compounds **7a**−**e** (1 equiv) were dissolved in 1 M HCl in MeOH (3 mL/mmol) and stirred at room temperature for 2 h. The mixture was then neutralized with $NaHCO_3$ (aq). The volatile solvents were removed under vacuum, and the residue was dissolved in DCM and washed with water (×2). The organic layer was dried over $MgSO_4$ and concentrated, and the residue was purified by column chromatography (toluene/ethyl acetate 15:1). **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, $J_{HH} = 8.3$ Hz, 2H), 7.21 (d, $J_{HH} = 8.3$ Hz, 2H), 4.70 (s, 1H), 4.50 (s, 2H), 4.46−4.38 (m, 1H), 4.24 (t, $J_{HH} = 4.5$ Hz, 1H), 3.62−3.54 (m, 2H), 3.48−3.44 (m, 1H), 3.37 (s, 3H), 2.06−1.98 (m, 1H), 1.93−1.86 (m, 1H), 1.80 (d, $J_{HH} = 4.9$ Hz, 1H); MS (ESI) m/z 394.0 ([M + Na]$^+$ calcd for $C_{14}H_{18}BrN_3NaO_4^+$ 394.0).

4.4.5. Synthesis of 9a−e. General O-Methylation Procedure. Compounds **8a**−**e** (1 equiv) were dissolved in DMF. Methyl iodide (8 equiv) and Ag_2O (2 equiv) were added. The mixture was stirred in room temperature overnight. The reaction was quenched with $CHCl_3$, and the solids were filtered off. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography (toluene/ethyl acetate 15:1). **9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.45 (m, 2H), 7.23−7.18 (m, 2H), 4.99−4.96 (m, 1H), 4.50 (s, 2H), 3.79 (s, 3H), 3.60−3.56 (m, 2H), 3.50−3.44 (m, 1H), 3.39 (s, 3H), 3.33 (s, 1H), 2.20−2.12 (m, 1H), 2.09−2.03 (m, 1H); MS (ESI) m/z 452.1 ([M − CH_3 + ACN + H_2O + Na]$^+$ calcd for $C_{14}H_{17}BrN_3O_4^+$ 370.1).

4.4.6. Synthesis of Final Compounds 10a−e. General Hydrolysis Procedure. Compounds **9a**−**e** (1 equiv) were dissolved in

1,4-dioxane/0.5 M H_2SO_4 1:1 and heated to reflux. After complete reaction (~1 h according to TLC), the mixture was cooled to room temperature and then neutralized with Na_2CO_3 (aq). The volatile solvents were concentrated under vacuum. The residue was dissolved in DCM and washed with H_2O (×2). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (toluene/ethyl acetate 10:1). **10a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J_{HH} = 8.2 Hz, 2H), 7.21 (d, J_{HH} = 8.2 Hz, 2H), 5.30 (d, J_{HH} = 5.6 Hz 1H), 4.51 (s, 2H), 4.38−4.28 (m, 1H), 3.78−3.75 (m, 1H), 3.72−3.68 (m, 2H), 3.61−3.54 (m, 1H), 3.35 (s, 3H), 3.14 (d, J_{HH} = 5.9 Hz, 1H), 2.14−1.96 (m, 2H); MS (ESI) *m*/*z* 394.0 ($[M + Na]^+$ calcd for $C_{14}H_{18}BrN_3NaO_4^+$ 394.0).

4.4.7. Synthesis of 11a−e. General Oxidation Procedure. Compounds **10a−e** (1 equiv) was dissolved in DCM. At 0 °C pyridinium dichromate (1.5 equiv) and 4 Å molecular sieves powder were added. The mixture was stirred overnight in room temperature. The solids were filtered off. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography (toluene/ethyl acetate 10:1). **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J_{HH} = 8.4 Hz, 2H), 7.20 (d, J_{HH} = 8.4 Hz, 2H), 4.71−4.64 (m, 1H), 4.52 (s, 2H), 4.15 (dd, J_{HH} = 6.0, 8.1 Hz, 1H), 3.76 (d, J_{HH} = 1.8 Hz, 1H), 3.74 (s, 2H), 3.70−3.64 (m, 1H), 3.55 (s, 3H), 2.48−2.38 (m, 1H), 2.32−2.21 (m, 1H); MS (ESI) *m*/*z* 392.0 ($[M + Na]^+$ calcd for $C_{14}H_{16}BrN_3NaO_4^+$ 392.0).

4.4.8. Synthesis of 12a−j. General Lactone Opening Procedure. Compounds **11a−e** (1 equiv) and the amine (**I−IV**) (2 equiv) were dissolved in diisopropylethylamine. 2-Hydroxypyridine (2 equiv) was added, and the mixture was heated to 70 °C overnight. If needed, a few drops of DMF was added for solubility. The mixture was concentrated, and the residue was purified by column chromatography (toluene/ethyl acetate 6:1). **12a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J_{HH} = 8.3 Hz, 2H), 7.31−7.14 (m, 6H),7.19 (d, J_{HH} = 8.3 Hz, 2H), 7.00 (d, J_{HH} = 8.9 Hz, 1H), 4.46 (s, 2H), 4.36 (d, J_{HH} = 5.7 Hz, 2H), 4.34−4.28 (m, 1H), 3.88−3.80 (m, 2H), 3.63−3.51 (m, 2H), 3.44−3.39 (m, 1H), 3.41 (s, 3H), 2.80 (bs, 1H), 2.44−2.34 (m, 1H), 2.10−2.02 (m, 1H), 1.90−1.83 (m, 1H), 0.96 (d, J_{HH} = 6.8 Hz, 3H), 0.91 (d, J_{HH} = 6.8 Hz, 3H); MS (ESI) *m*/*z* 576.2 ($[M + H]^+$ calcd for $C_{26}H_{35}BrN_5O_5^+$ 576.2).

4.4.9. Synthesis of Final Compounds 1a−l. General Procedure. Azides **12a−j** (1.0 equiv) were dissolved in MeOH and a few drops of water and then treated with Ph_3P (1.5 equiv). The mixture was stirred at room temperature overnight and then concentrated under vacuum. Without further purification the formed amine was used in the next step. 5-(Methanesulfonylmethylamino)-*N*′-(1-phenylethyl)isophthalic acid (**A**) or carboxylic acid **B** (1.0 equiv), Py-BOP (1.0 equiv), and DIPEA (1.0 equiv) were dissolved in DCM. The mixture was stirred at room temperature for 30 min before the amine (~1.5 equiv) from the previous reaction dissolved in DCM and DIPEA (1.0 equiv) was added. After complete reaction the mixture was washed with $NaHCO_3$ (×1) and brine (×1). The water phase was washed with DCM (×2). The organic layers were combined and dried over Na_2SO_4, concentrated under vacuum, and purified by column chromatography (toluene/ethyl acetate 1:1). **1a**: $[\alpha]_D^{20}$ −15.2 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.97 (t, J_{HH} = 1.4 Hz, 1H), 7.94 (t, J_{HH} = 1.4 Hz, 1H), 7.48−7.06 (m, 18H), 5.36−5.24 (m, 1H), 4.44 (s, 2H), 4.37−4.31 (m, 1H), 4.28−4.17 (m, 4H), 3.83−3.79 (m, 1H), 3.66−3.59 (m, 2H), 3.43 (s, 3H), 3.32 (s, 3H), 2.83 (s, 3H), 2.36−2.25 (m, 1H), 2.15−2.05 (m, 1H), 1.98−1.84 (m, 1H), 1.58 (d, J_{HH} = 6.8 Hz, 3H), 0.94 (d, J_{HH} = 6.8 Hz, 3H), 0.90 (d, J_{HH} = 6.8 Hz); HRMS (ESI) *m*/*z* 908.2898 ($[M + H]^+$ calcd for $C_{44}H_{55}BrN_5O_9S^+$ 908.2872).

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Supporting Information Available: Experimental details and structural characterization of all compounds and procedures for the synthesis of amine **I** and carboxylic acid **B**. This material is available free of charge via the Internet at http://pubs.acs.org.

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